

ONLINE FIRST

Comparison of Clonidine, Local Anesthetics, and Placebo for Pain Reduction in Pediatric Tonsillectomy

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Objective: To determine if pretonsillectomy injection of local anesthetics with and without clonidine reduces pain following tonsillectomy in children.

Design: A prospective, randomized, double-blind, placebo-controlled trial.

Setting: Tertiary care academic medical center.

Patients: A total of 120 children, ages 3 to 17 years, presenting for tonsillectomy.

Interventions: Patients were randomized to 1 of 3 pretonsillectomy injection groups: (1) saline, (2) lidocaine plus bupivacaine, or (3) lidocaine plus bupivacaine plus clonidine.

Main Outcome Measures: The total number of analgesic doses consumed on postoperative days (PODs) 1, 3, 5, and 7. Secondary outcome variables included total time and intravenous analgesic doses required in the recovery room, visual analog scale pain scores, and maximum tolerated diet on postoperative days 1, 3, 5, and 7.

Results: The total number of analgesic doses on PODs 1, 3, 5, and 7 were not significantly different between the

randomization groups ($P = .53$). The median numbers (interquartile ranges) of analgesic doses were 12.0 (9.0-16.8) for the lidocaine plus bupivacaine plus clonidine group, 12.0 (10.0-16.5) for the lidocaine plus bupivacaine group, and 14.0 (9.0-15) for the placebo group. The placebo group was found to have a more advanced diet on POD 1 ($P = .04$) and significantly less pain on POD 3 ($P = .02$). Multivariable analysis showed children in the lidocaine plus bupivacaine plus clonidine group were significantly less likely to need intravenous pain medication in the recovery room compared with children in the placebo group and again showed that the placebo group achieved a significantly more advanced diet and had less pain on PODs 1 and 3.

Conclusion: Pretonsillectomy injection of lidocaine, 1%, and bupivacaine, 0.5%, with or without clonidine (25 μ g) is not recommended for the reduction of posttonsillectomy pain.

Trial Registration: clinicaltrials.gov Identifier: NCT00678379

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TONSILLECTOMY WITH OR without adenoidectomy was performed in 530 000 US children younger than 15 years during 2006.¹

Much has been written on the benefits of tonsillectomy with respect to the postoperative improvement in a patient's quality of life and behavior.² Nonetheless, substantial morbidity occurs during the recovery period, including pain, dehydration, lethargy, and postoperative bleeding. These complications may require readmission to the hospital, most commonly for odynophagia and aversion to liquids leading to dehydration. Otolaryngologists and anesthesiologists have sought techniques and medications that will decrease these postoperative morbidities.

Many tonsillectomy studies have demonstrated benefits from perioperative local anesthetic injection, most frequently performed before the procedure to allow a preemptive blockade of the painful stimulus.³⁻⁹ Naja et al⁹ conducted a randomized controlled trial injecting a mixture of lidocaine, bupivacaine, fentanyl, and clonidine before tonsillectomy and were able to show significant benefits lasting 10 days. Prior to this study, Giannoni et al,⁴ using a pretonsillectomy injection of ropivacaine and clonidine, showed a significant decrease in early and late posttonsillectomy pain and medication use compared with placebo. These 2 studies showed a benefit beyond the day of surgery and duration of local anesthetic effect in contrast to most prior studies, which showed benefit only on the day of surgery.

In addition, many randomized controlled trials have shown no benefit from the use of local anesthetics during tonsillectomy.¹⁰⁻¹² However, the robust and long-lasting results seen in the trials combining clonidine and amide local anesthetics are promising and warrant further investigation. Our study was designed to validate and expand on these findings by using short-acting (lidocaine hydrochloride) and long-acting (bupivacaine hydrochloride) amide local anesthetics with and without clonidine hydrochloride to examine their effects on decreasing posttonsillectomy morbidity. Unlike many prior studies, our study was designed with adequate power such that a negative finding would be statistically significant.

METHODS

All pediatric patients aged 3 to 17 years who were scheduled for outpatient tonsillectomy with or without adenoidectomy with 1 of our participating surgeons (S.C., S.G., or R.L.) at our tertiary care medical center were screened for enrollment by a study physician. Exclusion criteria included diagnosis of obstructive sleep apnea (Apnea Hypopnea Index, ≥ 5); peritonsillar abscess; allergy to study medication; body mass index (calculated as weight in kilograms divided by height in meters squared) greater than 35; or any major systemic illness (eg, asthma, diabetes), genetic disorder, bleeding disorder, or diagnosed syndrome. Institutional review board approval was obtained, and an Investigational New Drug Application was submitted to the US Food and Drug Administration for the use of clonidine in this fashion (IND 101 179).

Demographic data collected included patient age, sex, race, and indication for performing tonsillectomy. Consent was obtained from all parents or legal guardians, and assent was obtained from the patient. For all patients, tonsillectomy with or without adenoidectomy was performed by 1 of the 3 attending surgeons (S.C., S.G., or R.L.) at our academic children's hospital. The anesthesia protocol included mask induction with sevoflurane, propofol (up to 3 mg/kg as needed for deep intubation), fentanyl titrated to maintain spontaneous ventilation (to a maximum of 0.5 μ g/kg), and glycopyrrolate (0.1 mg/kg). Patients were extubated spontaneously breathing but in a sedated state with a nasal trumpet or oral airway in place. All patients received 0.5 mg/kg of dexamethasone intravenously at the beginning of the procedure. Postoperative pain was managed with morphine sodium to a maximum of 0.2 mg/kg per dose, and nausea or vomiting was controlled with metoclopramide or ondansetron.

Patients were randomized to 1 of 3 groups in a double-blind fashion for pretonsillectomy injection: (1) normal saline (placebo); (2) lidocaine, 1%, and bupivacaine, 0.5%; or (3) lidocaine, 1%, bupivacaine, 0.5%, and 25 μ g of clonidine. Our institutional investigational pharmacy developed a block-of-6 randomization schedule to ensure adequate distribution among groups. Randomization numbers were kept in the investigational pharmacy and were not broken until all patients had completed the study. Syringes contained colorless study medications with a label including the study title, principal investigator (J.R.M.), and the patient's study number. A data collection chart was created for each patient, and a duplicate syringe label was placed on the chart. Preincisional infiltration was carried out by injecting 1.5 mL of the randomly assigned mixture into the peritonsillar mucosa on each side. Tonsillectomy did not begin until 5 minutes after injection and was performed using monopolar electrocautery. All persons (ie, physicians, operating room staff, recovery room staff, patients, and patients' families) were blinded to the study medication except for the in-

vestigational pharmacist who mixed the syringes at the time of the procedure. All patients were discharged home on a 7-day course of amoxicillin (azithromycin for penicillin-allergic patients), and hydrocodone (0.15 mg/kg/dose) with acetaminophen was provided for pain control.

The primary study end point was the cumulative number of analgesic pain medication doses given on postoperative days (PODs) 1, 3, 5, and 7. The study by Giannoni et al⁴ was used as the basis for our power calculation. Using a within-group standard deviation (SD) of 7, the study required 120 total patients, or 40 patients per group, to have 90% power, assuming a 2-sided type I error probability of 0.05 to detect a linear decrease of 50% between the placebo and lidocaine plus bupivacaine plus clonidine groups and 25% between the lidocaine plus bupivacaine and placebo groups. To account for pain medicine end points in the literature being different from the present study and possibly skewing sample size estimates, the mean and SD for the sample size were reassessed after half of the patients completed the study following the procedure proposed by Gould and Shih.¹³ This procedure can be carried out without unblinding of the groups. We did not have to adjust our sample size based on this calculation.

Secondary outcome variables included mean visual analog scale (VAS) scores using the Wong-Baker FACES pain rating scale¹⁴ at the time of discharge and on PODs 1, 3, 5, and 7. The Wong-Baker scale rates pain from 0, very happy, no hurt, to 10, the worst pain possible. We also evaluated maximum diet tolerated (not swallowing, liquids only, soft diet, regular diet) on PODs 1, 3, 5, and 7; mean doses of intravenous (IV) pain medication given in the recovery room; and mean time to discharge from the hospital. All adverse events were recorded. A data safety monitoring board was established to review all adverse events at the halfway point of the study and at completion.

The VAS score was estimated by a parent or legal guardian or by patients older than 10 years; previous data have shown this age to be a reliable cutoff for understanding a VAS.¹⁵ All procedures including enrollment, data collection on the day of surgery, and postoperative phone calls were performed by a study physician. At the time consent was obtained, parents were given a sheet to record postoperative doses of pain medication. In addition, a VAS scale was given to them and reviewed with them to facilitate data collection during phone calls. They were instructed to give the pain medication every 4 hours on an as-needed basis. The VAS scores on PODs 1, 3, 5, and 7 were recorded as the average for the previous 24 hours. Diet data were obtained by asking the legal guardian what the child's most advanced food item was for that day. All phone calls were made in the evening hours. Data were entered into the patient's paper medical chart and transferred to an online database created at our institution. All data were entered into the database on 2 separate occasions to ensure accuracy.

Statistical analysis was performed by 2 statisticians (D.B. and L.W.) using the software R 2.10.0 (The R project for Statistical Computing [http://www.R-project.org], November 2009). Study end points were compared between the placebo and active medication groups using the Kruskal-Wallis test as appropriate. The Mann-Whitney test and the Cochran-Armitage trend test were used to compare study end points of each treatment group to placebo. Secondary analysis included multivariable linear regression and proportional odds logistic regression models. The multivariable linear regression model was used to assess the association between time to discharge and treatment group after controlling for age, sex, ethnicity, and diagnosis. Log transformation was performed to achieve normality of residuals to satisfy regression assumptions. Proportional odds logistic regression models were used to estimate unadjusted and adjusted odds ratios (ORs) to evaluate the association between all other individual study end points and treatment groups af-

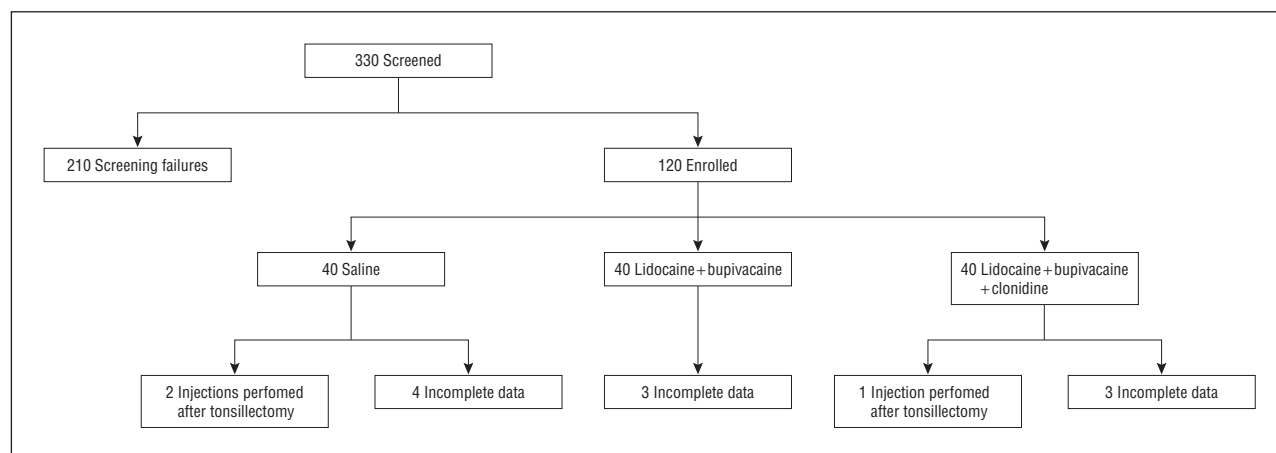


Figure 1. Flowchart.

Table 1. Characteristics of Participants by Study Group^a

Characteristic	Saline	Lidocaine + Bupivacaine	Lidocaine + Bupivacaine + Clonidine	P Value
Age, median (IQR)	6.0 (5.0-9.0)	7.0 (5.0-11.0)	8.0 (5.0-10.2)	.15 ^b
Sex				
Female	24 (60)	20 (50)	23 (57)	.64 ^c
Male	16 (40)	20 (50)	17 (42)	
Ethnicity				
White	32 (80)	32 (80)	30 (75)	.82 ^c
Other	8 (20)	8 (20)	10 (25)	
Diagnosis				
Adenotonsillar hypertrophy	14 (35)	12 (30)	15 (38)	.77 ^c
Chronic tonsillitis	26 (65)	28 (70)	25 (62)	

Abbreviation: IQR, interquartile range.

^aUnless otherwise indicated, data are reported as number (percentage) of participants.

^bKruskal-Wallis test.

^cPearson test.

ter controlling for the same covariates. Data are expressed as the median and interquartile range (IQR) for continuous variables, frequency and percentage for categorical variables. *P* values less than .05 were considered significant and were not adjusted for multiple comparisons.

RESULTS

A total of 330 patients were screened to enroll 120 during the period from April 7, 2008, through November 12, 2009 (**Figure 1**). Two patients in the placebo group and 1 in the lidocaine plus bupivacaine group had the injection performed after the tonsillectomy early in the enrollment period. Incomplete data were present for 4 patients in the placebo group, 3 in the lidocaine plus bupivacaine group, and 2 in the lidocaine plus bupivacaine plus clonidine group. Diagnosis groups included chronic tonsillitis, adenotonsillar hypertrophy, and sleep-disordered breathing. For analysis purposes, patients with a diagnosis of sleep-disordered breathing were included with the diagnosis of adenotonsillar hypertrophy. There were no differences in age, sex, race, or diagnosis among groups (**Table 1**).

The differences in median cumulative pain medication use on PODs 1, 3, 5, and 7 were not found to be sta-

tistically significant among randomization groups. The median numbers (IQRs) of doses per group were 14.0 (9.0-16.8) for lidocaine plus bupivacaine plus clonidine, 12.0 (10.0-16.5) for lidocaine plus bupivacaine, and 12.0 (9.0-15.0) for saline (**Table 2**). Our anticipated SD was 7, and the actual mean SD among the 3 groups was 4.7. A plot of the mean total analgesic doses with IQRs is shown in **Figure 2**. Comparison of the analgesic doses on each of PODs 1, 3, 5, and 7 did not differ between groups. There was also no statistical difference in the mean number of analgesic doses required in the recovery room or time to discharge.

The VAS scores did not differ between groups at discharge or on postoperative days 1, 5 or 7. On POD 3, the placebo group had significantly lower pain scores than the lidocaine plus bupivacaine plus clonidine group (*P* = .04). This comparison approached, but did not quite reach statistical significance on POD 1 (*P* = .06). There was no difference in VAS scores between the placebo and lidocaine plus bupivacaine group. **Figure 3** is a plot of the mean VAS scores over time.

The placebo group was significantly more likely to have an advanced diet on POD 1 than the lidocaine plus bupivacaine plus clonidine group (*P* = .04) but not the lidocaine plus bupivacaine group. There was no differ-

Table 2. Total Dose and Recovery Room Outcome by Study Group^a

Outcome	Saline	Lidocaine + Bupivacaine	Lidocaine + Bupivacaine + Clonidine	P Value ^b
Total analgesic doses	12.0 (9.0-15.0)	12.0 (10.0-16.5)	14.0 (9.0-16.8)	.53
Analgesic doses in recovery room	3.0 (3.0-5.0)	3.0 (2.0-4.0)	3.0 (2.0-4.0)	.22
Time to discharge, min	122 (90-188)	111 (81-142)	120 (79-175)	.43

^aUnless otherwise indicated, data are reported as median (interquartile range) values.

^bKruskal-Wallis test.

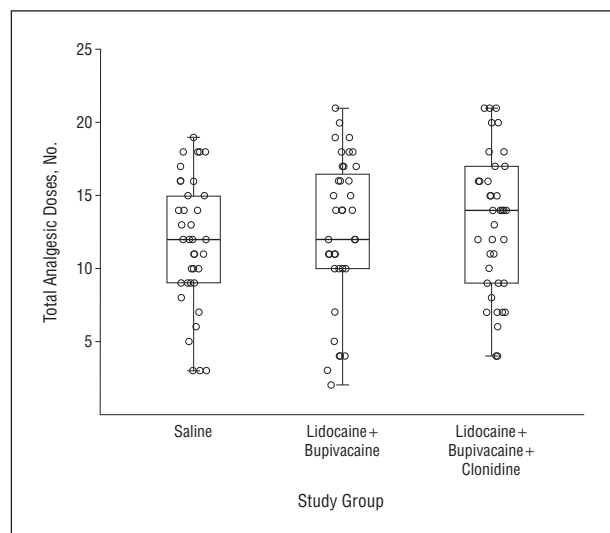


Figure 2. Mean total analgesic doses. Data points represent the total number of analgesic doses taken by a patient within each treatment group; thicker horizontal lines represent the overall mean numbers of analgesic doses taken by patients in each treatment group; rectangular boxes represent the interquartile ranges for each treatment group; thinner horizontal lines at the tops and bottom extremes of the graph represent the most and least, respectively, numbers of doses taken by patients in the treatment groups.

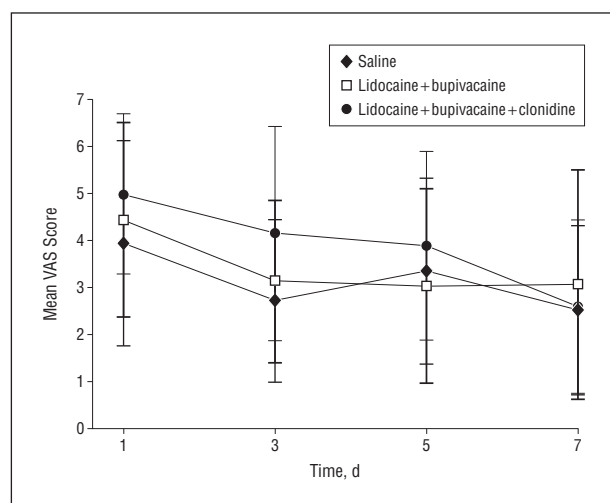


Figure 3. Mean visual analog scale (VAS) pain scores over time. Error bars represent standard errors.

ence on POD 3, 5, or 7. A plot of swallowing over time is displayed in **Figure 4**.

Proportional odds and multivariable regressions models were used to analyze outcome variables, while controlling for age, sex, ethnicity, and diagnosis. No dif-

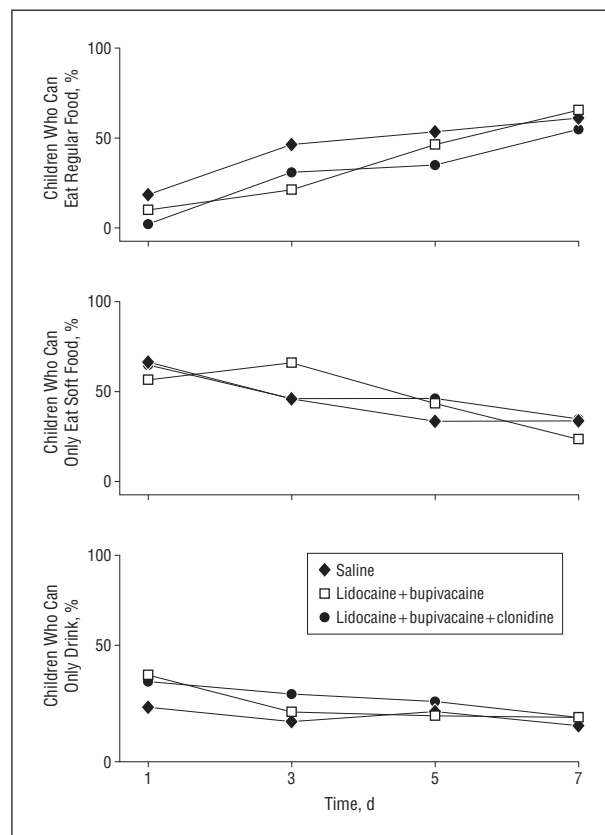


Figure 4. Daily swallowing ability.

ferences in total analgesic doses were found between groups when controlling for these variables. The multivariable regression model showed that children with a diagnosis of adenotonsillar hypertrophy and/or sleep disordered breathing took significantly less pain medication at all time points compared with those who had chronic tonsillitis. Children in the lidocaine plus bupivacaine plus clonidine group were significantly less likely to receive pain medication in the recovery room than were those in the placebo group (OR, 0.43 [95% confidence interval (CI), 0.19-0.99]). Diet was significantly more advanced in the saline group than in the lidocaine plus bupivacaine plus clonidine group on POD 1 (OR, 0.34 [95% CI, 0.13-0.90]) and POD 3 (OR, 0.39 [95% CI, 0.16-0.99]) and the lidocaine plus bupivacaine group on POD 3 (OR, 0.35 [95% CI, 0.14-0.87]). There was no significant difference in swallowing between randomization groups on POD 5 or 7. The proportional odds model showed that older children were signifi-

cantly more likely to be discharged earlier than younger children.

Adverse events are listed in **Table 3**. Patients in the lidocaine plus bupivacaine plus clonidine group and in the lidocaine plus bupivacaine group were more likely to be seen in the emergency department with dehydration. Children from the placebo group were seen with a history of postoperative bleeding more frequently than did children from the other treatment groups. Our rate of posttonsillectomy bleeding (4.5%) is consistent with previously reported data. Of note, bleeding in all patients resolved spontaneously, and no patients required intervention. One patient had a lingual nerve palsy that resolved 6 weeks after the tonsillectomy. Another patient was seen in the emergency department with severe pain only and was tolerating an oral diet.

COMMENT

The present study is an adequately powered, prospective, double-blind, randomized clinical trial designed to determine if pretonsillectomy injection of lidocaine, 1%, and bupivacaine, 0.5%, with or without clonidine (25 µg) decreases postoperative pain medication use. We chose to power our study based on a 50% decrease between the placebo and local anesthetic with clonidine group because we wanted to detect a difference that would lead to a change in clinical practice if found to be statistically significant. Based on our anecdotal observations and a thorough review of the literature, we anticipated a significant improvement in postoperative end points between the 2 local anesthetic groups compared with placebo. Attesting to this preconceived perception of benefit from local anesthetic injection, our senior surgeon (J.W.) declined to enroll patients because he believed that the use of placebo was below the standard of care. Owing to the unexpected results, an investigation was conducted to confirm the integrity of the randomization, and it was found to be accurate. Based on these findings, this surgeon no longer injects local anesthetics for his tonsillectomy patients.

Conflict has existed from the earliest publications of prospective literature on the use of local anesthetics for the relief of posttonsillectomy morbidity. In 1989, Broadman et al¹⁶ found no difference in postoperative pain scores or analgesic requirements when comparing bupivacaine plus epinephrine with placebo. Among the most quoted studies reporting a positive effect are those by Jebeles et al^{6,7} in 1991 and 1993, which compared pretonsillectomy injection of bupivacaine plus epinephrine with saline plus epinephrine. Both studies used a lower concentration but larger volume of bupivacaine than our study to show a significant decrease in pain with bupivacaine infiltration. However, both studies were limited by sample size and study design.

The findings of decreased postoperative morbidity following tonsillectomy by Jebeles et al^{6,7} have been validated by several other randomized trials. In a 2007 randomized study by Unal et al,¹⁷ a pretonsillectomy injection of local anesthetics led to improved end points in the 2 hours following tonsillectomy compared with placebo. Akoglu

Table 3. Adverse Events by Study Group^a

Adverse Event	Saline	Lidocaine + Bupivacaine	Lidocaine + Bupivacaine + Clonidine
Dehydration, 8% (n=9)			
Emergency department only	1	3	3
Admitted	0	1	1
Bleeding, 5% (n=5)	3	1	1
Intervention	0	0	0
Lingual nerve palsy	0	0	1
Severe pain	0	1	0

^aAll data reported as number of events.

et al¹⁸ also showed a significant reduction in time to first oral intake and pain up to 24 hours in children randomized to bupivacaine or ropivacaine vs those given placebo. Yilmaz et al¹⁹ randomized children to posttonsillectomy topical application of levobupivacaine and showed a significant decrease in pain scores up to 24 hours. These studies only evaluated children for the first 24 hours, and no long-term data were gathered. Most positive studies have shown the significant advantage to be in the early postoperative period. Using multivariable analysis, we found a significantly decreased likelihood for needing IV analgesics in only the lidocaine plus bupivacaine plus clonidine group over placebo, but there was no difference in VAS scores or time to discharge. Beyond the day of surgery, this early benefit was nullified when the lidocaine plus bupivacaine plus clonidine group was found to have a significantly less advanced diet than the placebo group on PODs 1 and 3 and significantly more pain on POD 3.

Other prospective randomized studies have shown a lack of benefit in reducing posttonsillectomy morbidity with the use of local anesthetics. In 2000, Hollis et al²⁰ reviewed 6 randomized trials of patients undergoing tonsillectomy who received local anesthetic before or after tonsil removal. None of the reviewed studies showed a significant difference between intervention and control groups other than outcome measures that were deemed inappropriate (eg, global pain score). Gemma et al²¹ randomized children to injection with ropivacaine or saline and showed no difference at 6 and 24 hours in pain scores or the number of pain medication doses after tonsillectomy.

Two studies demonstrated a benefit lasting well beyond the day of surgery with the addition of clonidine to local anesthetics. Giannoni et al,⁴ using a higher concentration and larger volume of local anesthetic than used in our study, found a significantly increased need for fentanyl and increased VAS score in the placebo group during the immediate postoperative period. The ropivacaine plus clonidine group, but not the ropivacaine only group, had a significant reduction in VAS pain scores on PODs 3 and 5 and a significant reduction in cumulative pain medication use on POD 5 compared with placebo. Similar results were found by Naja et al^{8,9} in 2 studies using a modified infiltration technique before tonsillectomy. Once again, the group of children receiving a mixture including bupivacaine and clonidine had significantly less pain and decreased need for analgesia from the day of

surgery to 10 days after tonsillectomy. These findings were the basis for the addition of clonidine to our local anesthetic combination of bupivacaine and lidocaine, although we used a lower dose of clonidine owing to the volume restriction of our syringes. In our study, the addition of clonidine resulted in a significant early postoperative benefit, but we found that these children fared significantly worse on PODs 1 and 3 compared with children in the placebo group. All children had equivalent VAS scores and were swallowing at the time of discharge. There was no difference seen beyond POD 3.

Using multivariable analysis, we found that older children and those with a diagnosis of adenotonsillar hypertrophy and/or sleep disordered breathing performed better after tonsillectomy, but our study was not powered to draw a conclusion on these differences. Our incidence of adverse events is in agreement with previously published data. Interestingly, those in the local anesthetic groups were more likely to be seen in the emergency department with dehydration, while those in the placebo group were more likely to be seen with bleeding.

The prospective, randomized, double-blind, placebo-controlled design of our study contributes to its validity. However, we acknowledge potential limitations. It is not known what the ideal dose of lidocaine, bupivacaine, or clonidine is for perioperative tonsillectomy injection. We did not weight base our dosing of these medications, and this may have contributed to its lack of efficacy. Given previous severe adverse events using local anesthetic injections during tonsillectomy, we did not use weight-based dosing of medications, limiting our volume to 1.5 mL per tonsil, and we did not include epinephrine. Giannoni et al⁴ used 50 µg of clonidine, while we used only 25 µg owing to volume restriction. The addition of epinephrine or an increase in volume or local anesthetic concentration might have resulted in a measurable benefit despite the potentially worse outcomes of these groups in our study.

If, as our findings suggest, the injection of local anesthetics is truly not beneficial, the cost savings will be significant. A conservative estimate assumes that 50% of otolaryngologists inject local anesthetics in their pediatric tonsillectomy cases, which represents 265 000 injections per year. At our institution, a syringe containing only local anesthetics costs the patient \$250. If these injections were no longer performed, a potential cost savings of \$66.25 million per year would result. At a time of fixed and even decreasing reimbursements for surgical procedures, this amount is not insignificant.

In conclusion, children in our study receiving a pretonsillectomy injection of lidocaine, 1%, and bupivacaine, 0.5%, with or without clonidine (25 µg) have no advantage over children receiving only placebo in the amount of postoperative pain medications required to control pain. We do not recommend pretonsillectomy injection for reducing morbidity in pediatric tonsillectomy patients. Based on the results of our study, we have changed the practice at our institution to no longer inject local anesthetics during tonsillectomy.

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